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Monkeypox: Insights into virus morphology, clinical manifestations, and mitigation strategies in developing nations

Ram Bahadur Khadka[1*]; Khimdhoj Karki[1]; Gautam Prasad Chaudhary[2]; Jitendra Pandey[3]

[1]Department of laboratory science, Crimson College of Technology, Affiliated with Pokhara University, Butwal-11, Devinagar, Rupandehi, Nepal; [2]Department of Pharmacy, Crimson College of Technology, Affiliated with Pokhara University, Butwal-11, Devinagar, Rupandehi, Nepal; [3]Department of Chemistry, University of Hawai'i at Manoa, 2545 McCarthy Mall, Honolulu, HI 96822, USA

[*]Corresponding author E-mail: rambahadurkhadka00@gmail.com

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Abstract

Monkeypox is an emerging zoonotic disease caused by the monkeypox virus (MPXV) and shares similarities with the other *Orthopoxviruses*. This review aimed to explore the morphology of MPXV, clinical manifestations, and mitigation strategies in the developing nations. Clinically, MPXV resembles smallpox. It has an unidentified natural host, despite it has been isolated from the rope squirrels and *Sooty mangabeys*. Transmission occurs through the respiratory excretions, saliva, contact with lesions, and potentially via the feces. The disease comprises a prodromal phase and subsequent skin rash. Originating in 1959 following a monkey outbreak in Copenhagen's research institute; the initial human case was documented in 1970 in the Democratic Republic of Congo. The virus subsequently dispersed globally; impacting several nations such as UK, USA, Israel, and Singapore. Thus, in addition to the healthcare infrastructure, combating monkeypox in the developing countries requires bolstering the disease surveillance, public awareness, diagnostic capabilities, and vaccination campaigns. Sustainable international collaboration and extensive scientific investigations are crucial for safeguarding the public health and preventing further spread of this viral disease.

Keywords: Monkeypox, Zoonotic disease, *Orthopoxviruses*, Clinical manifestations, Mitigation strategies

1. Introduction

Monkeypox (MPX) is an emerging zoonotic disease caused by the monkeypox virus (MPXV), a member of the genus *Orthopoxvirus* that belongs to the family *Poxviridae* (Petersen *et al*., 2019). MPXV shares similarities with the other *Orthopoxvirus* species that are pathogenic to humans, such as smallpox (now eradicated), cowpox, and vaccinia virus. However, it exhibits distinct clinical

characteristics (Petersen *et al*., 2019; Tiecco *et al*., 2022). Although, it has been isolated from a rope squirrel (from the Democratic Republic of Congo) and *Sooty mangabey* (from the Ivory Coast); the natural host of MPXV remains unknown. Transmission is believed to occur through the respiratory excretions; saliva, contact with lesion material, and potentially *via* feces (Petersen *et al*., 2019; Mileto *et al*., 2022). In 1959, MPXV was first identified during an outbreak in monkeys at a research institute in Copenhagen, Denmark. The first documented human case occurred on September 1, 1970, when a nine-month-old child was detected with a smallpox-like disease in Basankusu Hospital, the Democratic Republic of Congo (Aljabali *et al*., 2022; Chauhan *et al*., 2023). Between October, 1970 and May, 1971; six additional human cases were reported in Liberia, Nigeria, and Sierra Leone. In Nigeria, the first reported case emerged in 1971, followed by ten cases between 1971 and 1978. Since then, thousands of human monkeypox cases have been confirmed in fifteen different countries; primarily in Africa. Mostly the monkeypox cases have been occurred in the United Kingdom, United States, Israel, and Singapore (Alakunle and Okeke, 2022). Given the ongoing threat of monkeypox outbreaks; understanding the epidemiology, clinical manifestations, and control strategies is of utmost importance. The objectives of this comprehensive review were to provide a detailed analysis of monkeypox as well as examining several key aspects such as disease patterns and control strategies. By synthesizing an available knowledge, this review seeks to enhance the understanding and emphasizes the future interventions for effective management, prevention, and control of monkeypox outbreaks throughout the world.

2. Monkeypox virus

The appearance of MPXV is similar to other viruses in the *Orthopoxvirus* species (Pauli *et al*., 2010). The virus particles; known as virions, have an oval or brick-shaped structure. They are surrounded by a lipoprotein outer membrane that has a wrinkled or corrugated surface. The size of MPXV particles ranges from 200 to 250 nm (Forni *et al*., 2022). The outer membrane protects the core that contains enzymes, a double-stranded DNA genome and transcription factors (Lum *et al*., 2022; Wang *et al*., 2023a). The core is biconcave with lateral bodies on each side; however, this appearance is attributed to the way the core is observed under the electron microscopy (EM) (Luna *et al*., 2022). The MPXV genome is made up of a linear double-stranded DNA that is approximately 197 kb in length (Ghate *et al*., 2023). The ends of this DNA are joined together by hairpin-shaped structures called palindromic hairpins. The genome also contains inverted terminal repeats (ITRs), which are made up of hairpin loops, repeating sequences, and certain coding regions (Forni *et al*., 2022). MPXV is a DNA virus, but its entire life cycle takes place within the cytoplasm of the infected cells. All the necessary proteins for viral replication, transcription, assembly of new virus particles, and release from infected cells, are encoded by the MPXV genome (Luna *et al*., 2022; Wang *et al*., 2023a). The genes responsible for the basic functions are highly conserved among the *Orthopoxviruses*, and are located in the central region of the genome. Genes involved in the interactions between the virus and their hosts are less conserved and are found in the terminal regions (Petersen *et al*., 2019; Forni *et al*., 2022).

In the case of poxvirus-infected cells, there are two forms of the produced infectious virus particles; mainly intracellular mature virus (IMV) and extracellular-enveloped virus (EEV) (Likos *et al*., 2005; Wang *et al*., 2023a). IMV is released when the infected cell bursts, while EEV is released from the cells by interacting with the actin tails; thus, allowing the virus to spread quickly within the infected host. Other types of the virus particles are termed cell-associated virions (CEVs) that are formed when the intracellular enveloped virus (IEV) is transported to the cell surface using microtubules. The outer membrane of the IEV fuses with the host plasma membrane and remains attached to the cell surface (Wang *et al*., 2023a). CEVs are responsible for spreading the virus from one cell to another. IEV is

formed when the IMV is wrapped by a double membrane derived from the cellular components, called early endosomes or the trans-Golgi network. In addition to the IEV exocytosis, another way of EEV formation is through budding of the IMV through the host plasma membrane (Likos *et al*., 2005). While some strains of the cowpox virus (CPXV) form occlusions within the cellular structures called A-type inclusions (ATIs); however MPXV does not form ATIs or sequester IMVs into the ATIs, which is attributed to a truncation in the ATI gene (Wang *et al*., 2023a). The defective virus particles that cannot cause infection are known as non-infectious dense particles (DPs) and they have been observed in the prototype vaccinia virus (VACV). However, this defect has not yet been reported for MPXV (Likos *et al*., 2005; Forni *et al*., 2022).

3. Suspected modes of transmission

Monkeypox virus (MPXV) can be transmitted through two main routes; mainly animal-to-human transmission and human-to-human transmission (Wang *et al*., 2023b). Inter-human transmission occurs through the respiratory droplets, contact with body fluids, contaminated environments or items, and direct contact with the skin lesions of an infected person (Bahadur Khadka *et al*., 2020; Martínez-Fernández *et al*., 2023). MPXV variants consist of two different clades known as Congo Basin clade and West Africa clade. The Congo Basin clade of MPXV is considered more virulent than the West Africa clade, contributing to a higher rate of inter-human transmission. Animal-to-human transmission is also known as zoonotic transmission that occurs through direct contact with the natural hosts of the virus and/ or consumption of infected hosts (Chauhan *et al*., 2023). Contact with blood, body fluids, and mucocutaneous lesions of an infected animal can also lead to zoonotic transmission (Chaix *et al*., 2022). Nosocomial transmission has been reported for both of the Congo Basin and West Africa clades of MPXV, while sexual transmission has been speculated in several cases where infected individuals have groin and genital lesions (Petersen *et al*., 2019; Martínez-Fernández *et al*., 2023). Currently, there are no reports of human-to-animal transmission of MPXV. Transmission of MPXV from human to human, as measured by secondary attack rates and serial transmission events is higher for the Congo Basin clade compared with the West Africa clade (Antunes *et al*., 2022). Through the epidemiological studies, the contagiousness of infection i.e. reproduction number (R0) for the Congo Basin clade falls within the range of 0.6 to 1.0; indicating the potential for sustained human-to-human transmission and persistence in the human population. Although, it is presumed to be lower than that of the Congo Basin clade, the R0 has not been estimated for the West Africa clade (Aljabali *et al*., 2022). This suggests that the sustained human-to-human transmission and persistence in the human population is less likely for the West Africa clade and outbreaks are more likely to result from the spillover events of the zoonotic hosts. Table (1) illustrates the suspected modes of transmission of MPXV to humans based on the available information reported by Chaix *et al*., (2022); Chauhan *et al*., (2023).

4. Clinical presentation and pathogenesis

The clinical presentation of MPXV resembles smallpox but is less severe and has an incubation period of 5 to 21 days; usually 7 to 14 days (Niu *et al*., 2023). Symptoms of MPXV infection may vary depending on different factors, including exposure characteristics, age, presence of conditions that alter the immune response, previous immunity to smallpox, and the viral strain (Ali *et al*., 2023; Wang *et al*., 2023b). MPXV clinical phase and prodromal illness are characterised by fever, headache, lymphadenopathy, back pain, myalgia, fatigue, occasional sore throat, cough, vomiting and/or diarrhea. The skin rash starts to appear after the fever and includes the evolution of skin lesions from macules to papules, vesicles, and pustules before crusting and scaling off (Chadha *et al*., 2022; Forni *et al*., 2022). The skin lesions can be painful and itchy, and multiple stages may exist simultaneously, which are shown in Table (2), as clinical phases and symptoms of MPXV.

Table 1. Suspected modes of transmission of Monkeypox virus to humans

Suspected modes of transmission of Monkeypox virus	Routes
Animal-to-human transmission	• Direct contact with natural viral hosts (e.g., monkeys and rodents); • Consumption of infected animal products.
Human-to-human transmission	• Respiratory droplets (Close contact with an infected person who coughs or sneezes); • Contact with body fluids; ➢ Direct contact with skin lesions or wound exudates of an infected person; ➢ Contact with contaminated objects, surfaces, or clothing.
Nosocomial transmission	• Transmission occurring within healthcare settings; • Contact with infected patients; contaminated equipment, and/ or contaminated surfaces.
Sexual transmission (Speculated)	• Possible transmission through sexual contact with an infected individual having groin or genital lesions.
Zoonotic hosts	• Natural reservoir animals (*i.e*, rope squirrels and *Sooty mangabeys*). • Contact with blood; body fluids, and/ or mucocutaneous lesions of infected animals.

Table 2: Clinical phases and symptoms of Monkeypox viral infection, which are depicted by Chaix *et al*., (2022); Niu *et al*., (2023); Ali *et al*., (2023)

Clinical Phase	
Prodromal illness symptoms	**Skin rash symptoms**
Fever	Evolution of rash
Intense headache	Macules (flat, discolored spots)
Lymphadenopathy (enlarged lymph nodes)	Papules (small raised bumps)
Back pain	Vesicles (fluid-filled blisters)
Myalgia (muscle aches)	Pustules (pus-filled blisters)
Fatigue	Crusting of lesions
Sore throat (occasionally)	Scaling off of crusts
Cough (occasionally)	Lesions are often painful and can be itchy
Vomiting or diarrhea (less frequently)	Lesions at different stages (macules, papules, vesicles, pustules) can be present simultaneously

The MPXV follows a similar path as the smallpox virus when it infects the body. Infection begins after the virus enters through the mouth or respiratory system of the host (Lum *et al*., 2022), and then it begins the reproduce at the site of entry. In the cases of human-to-human transmission, the virus replicates in the respiratory and oral mucosa (Wang *et al*., 2023b). After replication, the virus enters into the bloodstream and spreads to the nearby lymph nodes, which is called primary viremia. From there, the viral load can reach the distant lymph nodes and organs through the circulatory system, thus causing secondary viremia (Martínez-Fernández *et al*., 2023). This entire process is known as the incubation period, which usually lasts from 7 to 14 days; but can take up to 21 days (Lum *et al*., 2022; Ahmed *et al*., 2023).

During the incubation period, there are no visible signs or symptoms of MPXV and the infection is not contagious. The symptoms and clinical signs of MPXV become evident during the prodromal stage (Letafati and Sakhavarz, 2023). At this stage, the virus spreads from the lymphoid organs to the skin, lungs, eyes, and the gastrointestinal tract. The prodromal stage includes the period when the infected person is most infectious, mainly during the presence of several infection symptoms, such as skin lesions, swollen lymph nodes, and other nonspecific symptoms (Forni *et al*., 2022; Ali *et al*., 2023).

5. Mitigation strategies to battle MPXV in the developing countries

In response to the growing threats of MPXV outbreaks; many developing countries have recognized the importance of earlier preparation and have begun implementing the different mitigation strategies (Malik *et al*., 2023). These strategies include strengthening the surveillance systems to promptly detect the infection cases; enhancing the public awareness to promote early recognition of the disease symptoms, improving the laboratory facilities for accurate diagnosis, and prioritizing the vaccination efforts to protect the populations (Al-Tawfiq *et al*., 2022; Dukers-Muijrers *et al*., 2022). The developing nations are collaborating with the international organizations and sharing information with the other affected countries to gain insights into the successful control measures and best practices. By learning from each other's experiences, they aim to develop targeted approaches suited to their unique healthcare settings and resource limitations (Malik *et al*., 2023).

Successful implementation of MPXV mitigation strategies in the developing countries relies on the collaboration and support of the various stakeholders, including the governments, healthcare professionals, international organizations, and the public (Alakunle and Okeke, 2022; Peter *et al*., 2022). Coordinated efforts will be crucial in minimizing the impact of MPXV outbreaks, protecting the public health, and ensuring a safer and healthier future for all (Ahmed *et al*., 2023; Malik *et al*., 2023).

5.1. Strengthening the surveillance and early detection of the virus

In the developing countries, establishing and bolstering the disease surveillance systems is imperative to proactively detect and respond to the MPXV outbreaks. To achieve this, a robust network of surveillance points should be created, along with encompassing healthcare facilities, community health workers, and veterinary services (Al-Mandhari *et al*., 2022). By actively involving these key stakeholders, the information flow can be optimized, thus allowing for early detection and swift reporting of the suspected MPXV cases. Proper training of the healthcare workers and frontline personnel's' to recognize MPXV symptoms, including fever, headache, muscle aches, and rash with pustules, is crucial for early identification of the potential cases (Niu *et al*., 2023). Early detection allows for timely implementation of the containment measures, reducing the risk of widespread transmission, and mitigating the severity of the outbreak (Al-Mandhari *et al*., 2022).The developing countries can significantly enhance their

ability to detect and respond swiftly to MPXV cases, safeguarding the public health, and minimizing impact of the disease on the vulnerable populations, by investing in a robust disease surveillance system, prioritizing training, and by fostering collaboration among the healthcare providers, community workers, and veterinary services (Lahariya *et al*., 2022).

5.2. Public awareness and education

Public awareness and education are fundamental elements in combatting MPXV in the developing countries. Raising awareness about the disease's symptoms, transmission, and preventive measures empowers the individuals to early recognize the pathological symptoms and go for prompt medical attention (Hemati and Mohammadi-Moghadam, 2023). Educational campaigns can be disseminated through various channels, including mass media, community outreach programs, and social media platforms, to reach a broader audience (Lahariya *et al*., 2022). Elimination of misconceptions, addressing the misconceptions, public awareness campaign, always plays crucial role in reducing the stigma and fear associated with MPXV, thus promoting a supportive environment for the affected individuals. Furthermore; targeted education that focuses on the high-risk groups (*i.e*., the health care workers and those in close contacts with the animals) and equipping them with knowledge on the preventive measures and control, is another necessary step (Malik *et al*., 2023). During outbreaks, building trust in the healthcare system is vital to encourage the public's cooperation with the health authorities (Al-Mandhari *et al*., 2022). Additionally, public awareness fosters the behavioral changes encourages the adoption of preventive practices and leads to early reporting of the suspected cases. By creating a culture of preparedness and resilience the sustained public awareness efforts ensure a proactive response to combat MPXV and protect the public health (Srichawla *et al*., 2023).

5.3. Diagnostic capacity and laboratory support

In the developing countries; combatting MPXV requires a strong diagnostic capacity and robust laboratory support (Al-Tawfiq *et al*., 2022; Altindis *et al*., 2022). Establishing and strengthening the laboratory facilities for accurate diagnosis of MPXV cases is essential for timely identification and appropriate management. This involves ensuring access to the reliable diagnostic tests; adequate training of the laboratory personnel's, and adherence to the standardized protocols for samples collection and testing's (Aden *et al*., 2022). Moreover; fostering collaborations with the national and international reference laboratories during the outbreaks can provide a valuable support in confirming the viral cases. By enhancing the diagnostic capabilities and laboratory support; the developing countries can swiftly identify and respond to the MPXV cases, thus enabling effective containment measures and preventing further spread of the disease (Al-Tawfiq *et al*., 2022).

5.4. Isolation and contact tracing

Isolation and contact tracing are vital components in combatting MPXV outbreaks in the developing countries (Al-Mandhari *et al*., 2022).When suspected or confirmed cases of MPXV are identified, it is essential to promptly isolate the affected individuals to prevent further transmission of the virus. Isolation facilities should be designated and equipped to provide appropriate care, while minimizing the risk of spreading the disease to the others. Simultaneously, rigorous contact tracing should be initiated to identify and monitor the individuals who have been in close contact with the confirmed cases (Srichawla *et al*., 2023). By tracing and monitoring the contacts, the health authorities can quickly identify and isolate the potential new cases, break the chain of transmission, and prevent the spread of MPXV within the community (Adnan *et al*., 2022). These measures are crucial in controlling the outbreaks, reducing the number of viral cases, and safeguarding the public health under the resource-limited settings (Al-Mandhari *et al*., 2022).

5.5. Vaccination campaigns

Vaccination campaigns play a significant role in combating MPXV in the developing countries (Choudhary *et al*., 2022). Developing and implementing effective vaccines against MPXV can provide a preventive barrier, particularly for the high-risk populations. The spread of the viral disease can be curtailed by vaccinating the healthcare workers, veterinarians, and individuals in close contact with the animals (Mohamed *et al*., 2023). Additionally, targeted vaccination efforts in regions with previous MPXV outbreaks can help to building the immunity and reducing the severity of the future outbreaks (Dukers-Muijrers *et al*., 2022). Public awareness about the importance and safety of vaccination is crucial to encourage participation and achieve optimal vaccine coverage. Integrating vaccination campaigns with the existing immunization programs can further enhance the accessibility and ensure a more comprehensive approach to controlling MPXV under resource-constrained settings. By leveraging vaccination as a preventive measure, the developing countries can effectively mitigate the impact of MPXV outbreaks and protect their populations' health (Ortiz-Saavedra *et al*., 2022; Mohamed *et al*., 2023).

5.6. Strengthening the healthcare infrastructure

To combat MPXV effectively in the developing countries, strengthening the healthcare infrastructure is paramount. Investing in the healthcare facilities, equipment, and personnel's is essential to enhance the capacity to diagnose, treat, and manage MPXV cases (Sekaran *et al*., 2023). This includes establishing isolation units equipped with necessary medical supplies, ventilators, and protective equipment for the healthcare workers (Siddiqui *et al*., 2023). Furthermore, training the healthcare professionals on the recognition and management of MPXV, in addition to infection prevention and control measures, is crucial to ensure a prompt and effective response (Siddiqui *et al*., 2023). Strengthening the healthcare infrastructure also involves improving access to the healthcare services in remote and underserved areas; facilitating early detection and timely intervention (Al-Mandhari *et al*., 2022). By building resilient healthcare systems, the developing countries can better cope with the MPXV outbreaks and safeguard the health and well-being of their populations likewise what was performed during the COVID-19 pandemic (Khadka and Gyawali, 2020; Malik *et al*., 2023; Sekaran *et al*., 2023).

5.7. International collaboration

International collaboration is a key factor in combatting MPXV effectively in the developing countries (Siddiqui *et al*., 2023). Given the potential of cross-border spread and the global nature of the infectious diseases; cooperation between the different countries and the international health organizations is vital. Sharing information, best practices, and resources, can enhance disease surveillance, early detection, and response capabilities. The collaborative efforts may include joint research projects to understand the epidemiology of MPXV and develop effective control measures (Thornhill *et al*., 2022). International supports in the form of technical expertise, training programs, laboratory assistance, and financial aid, can strengthen the healthcare systems in the developing countries; thus, enabling them to effectively manage MPXV outbreaks. By fostering the international partnerships, the different countries can work together to mitigate the spread of MPXV, prevent its resurgence, and protect the global public health (Bustanji *et al*., 2023).

5.8. Animal surveillance and control measures

To combat the MPXV effectively in the developing countries, implementing the animal surveillance and control measures is crucial (Kumar *et al*., 2023). Given its zoonotic nature; monitoring and managing this viral disease in the animal populations is essential for preventing its human transmission (Al-Tawfiq *et al*., 2022). The developing countries should establish comprehensive animal surveillance programs to detect MPXV in the wildlife and domestic animals. Close collaboration between the human and veterinary health authorities is essential for timely reporting and investigating the suspected animal cases.

Implementing the control measures, such as quarantining the infected animals, restricting movement of the animals from the affected areas, and implementing the vaccination campaigns for the susceptible animal populations can help to breaking the transmission cycle and reducing the risk of spillover to humans. By actively addressing the disease at its animal source, the developing countries can reduce the impact of MPXV outbreaks on both of the human and animal health (Siddiqui *et al*., 2023; Sekaran *et al*., 2023).

5.9. Travel restrictions and border control

To combat MPXV in the developing countries, implementation of the travel restrictions and stringent border control measures can be effective in limiting the spread of this disease. Travel-related cases can lead to the introduction of MPXV into new regions, thus exacerbating outbreaks (Sah *et al*., 2022).The developing countries should collaborate with the international health organizations and neighboring countries to establish surveillance at the points of entry, such as the airports and the land borders. Screening measures, including health questionnaires and temperature checks can help to identifying the travelers showing symptoms of MPXV (Farahat *et al*., 2022; Sekaran *et al*., 2023).The suspected cases should be isolated immediately and then a contact tracing should be initiated for the potential exposures. By promptly detecting and containing MPXV cases at the borders, the developing countries can prevent the importation of MPXV and reduce the risk of large-scale outbreaks; thus, protecting the public health and ensuring a coordinated response to the disease (Siddiqui *et al*., 2023).

5.10. Research and data collection

In the developing countries, the research and data collection is essential in combating MPXV (Rao *et al*., 2022). Conducting thorough research on the epidemiology, transmission dynamics, and risk factors in the developing countries helps in better understanding of the disease. Long-term surveillance studies can provide valuable insights into the disease's trends; patterns, and potential sources of outbreaks. Collecting accurate and comprehensive data on MPXV cases, including demographic information; clinical features, and outcomes, enables evidence-based decision-making and targeted interventions (Besombes *et al*., 2022). By investing in research and data collection, the developing countries can strengthen their disease surveillance systems, improve outbreak preparedness, implement effective control measures to minimize the impact of MPXV on the public health, and ultimately protect their populations from the disease (Zeeshan *et al*., 2022).

Conclusion

Monkeypox remains a significant public health concern in the developing countries; thus, necessitates the implementation of effective strategies to combat the disease and protect the vulnerable populations. This comprehensive review has highlighted several key aspects of MPXV, including its morphology, clinical manifestations, and the crucial roles of the different mitigation strategies in the developing nations. To effectively combat MPXV, the developing countries must focus on strengthening the disease surveillance and early detection systems. Establishing a robust network of surveillance points involving healthcare facilities; community health workers and veterinary services, enables prompt identification and response to MPXV outbreaks. The public awareness and education campaigns are essential to reduce the stigma, promote early recognition of the disease symptoms, and encourage the preventive practices. Furthermore, enhancing the diagnostic capacity, vaccination campaigns, and healthcare infrastructure will play pivotal roles in controlling MPXV transmission and safeguarding the public health. By fostering the international collaboration, sharing knowledge, and investing in research; the developing countries can build resilient responses to combat MPXV outbreaks and ensure a safer and healthier future for their populations.

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Conflict of interest

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Ethical approval

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Authors' Contributions

Conceptualization, R.B.K. and J.P.; Data curation, R.B.K. and G.P.C.; Investigation, R.B.K. and K.K; Supervision, R.B.K. and J.P; Validation, R.B.K. and K.K.; Roles/Writing – original draft, R.B.K. and J.P.; Writing- review & editing, R.B.K. and G.P.C.

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